Applicants respectfully disagree and traverse. Nonetheless, Applicants have amended claims 38 and 39 to read "an isolated heterodimer comprising the isolated polypeptide" of claims 24 or 31, respectively. Support for the amendment to the claims can be found for example, at page 76, line 14, through page 77, line 8. Accordingly, Applicants respectfully request that the rejection of claims 38 and 39 under 35 U.S.C. 112 be reconsidered and withdrawn.

II. Rejections under 35 U.S.C. §112, first paragraph

A. The Examiner rejected claims 24-101 under U.S.C. § 112, first paragraph, for lack of enablement.

More particularly, the Examiner alleges that:

> The specification does not provide any working examples that the polypeptide functions as recited in the claims, and limited guidance. It is not predictable, based on limited regions of homology to proteins with known functions, what activities the polypeptide of the invention has.

Applicants respectfully disagree and traverse.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. M.P.E.P. § 2164.01(a). Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 443 F.2d 1386, 1390-1391, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). As mentioned by the Examiner, the factors that can be considered in determining whether an amount of experimentation is undue have been set forth in *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of

working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *See id.*

In re Wands involved an appeal from the Board of Appeals and Patent Interferences, affirming the Examiner, rejecting immunoassay claims on the grounds that making anti-HBsAg antibodies for use in the claimed immunoassay, other than the deposited antibody, would be unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies. *Id.* at 735, 8 U.S.P.Q.2d at 1402. Antibodies other than the one deposited were described only in terms of function and only a general method of making and using them was disclosed in the application. *See id.* The facts showed that IgM antibodies were disfavored because they tended to self-aggregate and precipitate, isolating the correct antibodies required screening hundreds of clones, and the appellant's first four attempts were unsuccessful. *See id.* at 734, 8 U.S.P.Q.2d at 1402. Nevertheless, the Federal Circuit found that the disclosure satisfied the requirements under 112 first paragraph. The court based its decision on the fact that the invention could be practiced with readily available starting materials using methods that are well known in the monoclonal antibody art and because practitioners of the art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. *See id.* at 736, 8 U.S.P.Q.2d at 1406.

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, in *In re Angstadt,* the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

537 F.2d at 503, 190 U.S.P.Q. at 219 (emphasis in the original). As Judge Rich explained in *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Applicants submit that, in the instant case, since the disclosed or otherwise known methods of making and screening the claimed polypeptides may be used to determine, without undue experimentation, whether a given polypeptide encompassed by the claims functions, for example, as a cytokine receptor (see, *e.g.*, page 10, lines 23-25), or in activating the Jaks-STAT signal transduction pathway (see, *e.g.*, page 9, line 16, and Example 13, particularly, page 147, line 12), or in regulating the differentiation and/or proliferation of cells (see, *e.g.*, page 9, lines 19-23), or to routinely generate CRCGCL specific antibodies which could be used as immunological probes for differential identification of tissue(s) or cell type(s) (see, *e.g.*, page 10, lines 15-17), the enablement requirement is fully satisfied. *In re Wands*, 858 F.2d at 738, 8 U.S.P.Q.2d at 1404; *Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1906-1907 (B.P.A.I. 1989).

With respect to the Examiner's allegation:

> The skilled artisan would not know what functions or activities polypeptides that are 90-95% identical to the polypeptides disclosed in the specification would retain, or polypeptides that can have from one to 30 amino acid substitutions to those polypeptides.

Applicants submit that the proper inquiry is not whether the specification teaches how to make and use all of the polypeptides encompassed by the claims, but rather, whether

polypeptides encompassed by the claims have at least a single use, and this use can be confirmed, without undue experimentation, by following procedures either described in the specification or otherwise known in the art. See *In re Angstadt*, 537 F. 2d 498, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976):

> To require such a complete disclosure would apparently necessitate a patent with "thousands of examples . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments . . .

Further, as Judge Rich explained in *In re Vaeck*, 947 F. 2d 488, 20 U.S.P.Q.2d 1438, 1445 (Fed.Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to *determine,* without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis provided). Since, as discussed above, the disclosed or otherwise known methods of making and screening polypeptides (including variants and fragments) may be used to make and then determine, without undue experimentation, whether a given polypeptide encompassed by the claims is able to function, as a cytokine receptor, or in activating the Jaks-STAT signal transduction pathway, or in regulating the differentiation and/or proliferation of cells, or to routinely generate CRCGCL specific antibodies which could be used as immunological probes for differential identification of tissue(s) or cell type(s) and therefore possesses a disclosed utility, the enablement requirement is fully satisfied. *In re Wands*, 858 F. 2d 731, 8 U.S.P.Q. 2d at 1404; *Ex parte Mark*, 12 U.S.P.Q. 2d 1904, 1906-1907 (B.P.A.I. 1989).

Further, Applicants submit that, in the present case, the claimed polypeptides which share 90-95% identity with SEQ ID NO:2 would be particularly useful, for example, in epitope-mapping, in routinely generating CRCGCL specific antibodies which could be used as immunological probes for differential identification of tissues(s) or cell type(s) (see, *e.g.*, page 10, lines 15-17), or in immunoassay techniques, routine in the art, to detect the

polypeptides of the present invention. Polypeptide fragments of at least 30 contiguous amino acids in length, would be useful in routinely generating antibodies against CRCGCL polypeptides (see, *e.g.*, page 59, line 29, through page 61, line 13; and pages 140-143). It is noted that it was well known in the art on the priority date of the present application that antibodies can be made to polypeptide fragments even though they may not be immunogenic in an animal using methods such as phage display (as disclosed at page 59, lines 8-12).

The specification teaches which amino acid residues comprise epitope-bearing portions of CRCGCL (see, *e.g.*, page 60, lines 1-2). With this information, one of ordinary skill in the art would know which amino acid residues of the polypeptide could be substituted and still constitute a polypeptide which is capable of raising antibodies to CRCGCL. For example, amino acids +1 to +371, as recited in claim 22(a), comprise an epitope bearing portion at amino acids +286 to +293. If up to 37 amino acids (10% of the total amino acids present between +1 and +371) were to be substituted within the sequence of amino acids between +1 and +371, one of ordinary skill in the art would know not to substitute amino acids +286 to +293 in order to produce a polypeptide which is still useful for raising antibodies to this epitopic region of CRCGCL. Thus, the above shows that one of ordinary skill in the art could routinely determine which amino acids could be substituted without further changing the utility of the polypeptide as related to raising antibodies which could be used, for example, as immunological probes for differential identification of tissues(s) or cell type(s).

The Examiner cites Bowie et al. as support for her contention that "[g]enerally, the art acknowledges that function cannot be predicted based on structural information alone."

Applicants submit that this reference which is cited by Applicants at page 20, lines 2-6, of the specification is also adequate in giving one skilled in the art guidance concerning which amino acid changes are phenotypically silent. Moreover, Applicants provide examples

of conservative and nonconservative amino acid replacements at each position of SEQ ID NO:2 in the specification as filed (see, *e.g.*, pages 21, line 1 through page 35, line 26). In addition, the specification discloses Cunningham and Wells, *Science 244:*1081-1085 (1989) which teaches how to determine which amino acids of a protein are essential to its function (see, *e.g.*, page 20, lines 15-20). Applicants believe that these disclosures are sufficient to enable one skilled in the art to make amino acid substitutions, deletions, and insertions up to 10% of the total number of amino acids provided without changing the utility of the polypeptide.

In view of the above discussion, Applicants believe the Examiner's concerns have been fully addressed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 24-10 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

B. The Examiner rejects claims 31-39, 51, 53, 59-63, 76-87, 94-99 and 101 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

More particularly, the Examiner states that "[t]he enablement of claims 31-39, 51, 53, 59-63, 76-87, 94-99 and 101 requires availability of the specific clones claimed therein."

Thus, to demonstrate full compliance with 37 C.F.R. §§ 1.803-1.809 and to satisfy the requirement of 35 U.S.C. § 112, first paragraph, the undersigned Attorney hereby states that ATCC Deposits Nos. 209691 and 209641 of clone HTAEK53 have been deposited under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure with the following International

Depository Authority: American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110-2209, USA.

In accordance with MPEP § 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Deposit Nos. 209691 and 209641, will be irrevocably removed upon the grant of a patent based on the captioned application, and that these deposits will be replaced if viable samples cannot be dispensed by the ATCC, except as permitted under 37 C.F.R. § 1.808(b).

In view of the above discussion, Applicants believe the Examiner's concerns have been fully addressed. Accordingly, Applicants respectfully request that the rejections of claims 31-39, 51, 53, 59-63, 76-87, 94-99 and 101 under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

III. Rejections under 35 U.S.C. §102

The Examiner rejects claims 40, 43 and 46 under 35 U.S.C. 102(b) as allegedly being anticipated by Sugamura et al., EP 0578 932 A2, Jan. 19, 1994.

More particularly, the Examiner contends:

> Sugamura et al. disclose a polypeptide (SEQ ID NO:4) comprising an amino acid sequence that is identical to amino acids 54-57 (m=54, n=57), 81-84 (m=81, n=84) and amino acids 150-153 (m=150, n=153) of SEQ ID NO:2 (amino acids 61-64, 90-93 and 165-168, respectively of SEQ ID NO:4), and a composition comprising the polypeptide and a pharmaceutically acceptable carrier (claim 34).

Applicants respectfully traverse the rejection under U.S.C. § 102(b).

Nonetheless, solely in the interest of facilitating prosecution, Applicants have amended claim 40(c) by adding the language "wherein said amino acid sequence comprises at least seven contiguous amino acid residues of SEQ ID NO:2" thereby obviating the rejection over Sugamura et al. Support for the amendment to the claim can be found, for

example, at page 60, lines 17-26. Accordingly, Applicants respectfully request that the rejection of claims 40, 43 and 46, under 35 U.S.C. 102(b) be reconsidered and withdrawn.

IV. Conclusion

In view of the foregoing amendments and remarks, applicants believe that this application is now in condition for allowance.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: 1/05/01

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Enclosures

EOA 1/17/01
a/true

APPENDIX A – Marked up copy of Amended Claims

38. (Once amended) An isolated heterodimer comprising [The] the isolated polypeptide of claim 24 [comprising a heterodimer].

39. (Once amended) An isolated heterodimer comprising [The] the isolated polypeptide of claim 31 [comprising a heterodimer].

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40. (Once amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence comprising residues m to 371 of SEQ ID NO:2, where m is an integer in the range of +2 to +370;

(b) an amino acid sequence comprising residues 1 to n of SEQ ID NO:2, where n is an integer in the range of +2 to +371; and

(c) an amino acid sequence comprising residues m to n of SEQ ID NO:2, ~~where m is an integer in the range of +2 to +370 and n is an integer in the range of~~ +2 to +371; and wherein said amino acid sequence comprises at least seven contiguous amino acid residues of SEQ ID NO:2.